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The role of the hippocampus and dorsolateral prefrontal cortex in implicit learning of contextual information.

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LIST OF ABBREVIATIONS

BBA	Beta-band activity
BOLD	Blood oxygen level-dependent response
cTBS	Continuous theta-burst stimulation
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
FEFs	Frontal eye fields
FIR	Finite impulse response
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GRAPPA	GeneRalized Autocalibrating Partial Parallel Acquisition
HEOG	Horizontal electrooculography
HPC	Hippocampus
ICA	Independent component analysis
ICM	Implicit contextual memory
IPs	Intraparietal sulcus
MEP	Motor-evoked potential
MNI	Montreal Neurological Institute
MPRAGE	Magnetization-prepared rapid gradient echo
MRI	Magnetic resonance imaging
MT	Motor threshold
MTL	Mediotemporal lobe
PFC	Prefrontal cortex
PTSD	Post-traumatic stress disorder
RTs	Reaction times
TFRs	Time-frequency representation
TMS	Transcranial magnetic stimulation
TPJ	Temporoparietal junction
VEOG	Vertical electrooculography
VFC	Ventral frontal cortex
vPPC	Ventral posterior parietal cortex

1 GENERAL INTRODUCTION

1.1 Overview of contextual memory

The perception and interaction with the objects in the real world involves the use of unified relations between the object, surrounding related objects, and associated environments, which are commonly named contextual frames or contextual representations. Contextual frames may include temporal, cognitive, social, interoceptive and spatial associations (Maren, Phan, & Liberzon, 2013). In particular, spatial associations refer to locations where objects can be found, places where things happen or spatial relations between elements (Aminoff, Kveraga, & Bar, 2013).

Contexts are spontaneously and quickly encoded when subjects interact repeatedly with elements which tend to co-vary with each other. Importantly, once a context has been encoded, subsequent interaction with a subset of those elements reactivates the whole network of elements that define the context (Aminoff et al., 2013). Thus, a key feature of contextual memory is that it provides efficient and flexible neural representations of the environment, which have an important predictive value necessary for adaptive behavior. In the light of the above, there is evidence that contextual memories provide a set of expectations that in some circumstances are crucial to facilitate perceptions (Bar, 2004). For instance, objects that are presented in expected contexts are recognized more quickly than objects presented in unexpected contexts (Palmer, 1975). Similarly, ambiguous objects become recognizable if they are presented in appropriate contexts (Torralba, 2003; Bar, 2004). More recent studies have suggested that both implicit and explicit contextual memory play an important role in guiding attention to the expected location of relevant stimuli. For example, during visual search, targets are found more quickly when they are embedded in a repeated configuration of objects than when they are embedded in a novel configuration (Chun & Jiang, 1998; Bennett, Barnes, Howard, & Howard, 2009). In addition, targets are found more rapidly when they

appear at a location containing temporal regularities (Hutchinson & Turk-Browne, 2012; Zhao, Al-Aidroos, & Turk-Browne, 2013). Moreover, recent findings suggest that contextual memory may be important in the development of mental disorders such as post-traumatic stress disorder (PTSD), where deficits in processing contextual information have been assumed (Rudy, Huff, & Matus-Amat, 2004; Brewin, Kleiner, Vasterling, & Field, 2007; Lang et al; 2009; Acheson, Gresack, & Risbrough, 2012). Thus, contextual memory is a powerful neurocognitive mechanism essential for generating predictions (Bar & Ullman, 1996; Bar, 2004), guiding attention (Chun & Jiang, 1998; Moore, Laiti, & Chelazzi, 2003; Bennett et al., 2009; Kristjánsson & Campana, 2010; Stokes, Atherton, Patai, & Nobre, 2012; Hutchinson & Turk-Browne, 2012; Zhao et al., 2013), and ultimately to construct meaning. Despite the potential importance of contextual memory in cognition, its neural mechanisms have been little studied.

1.2 Implicit contextual memory and attentional control

Decades of research into the neurocognitive mechanisms of attention have revealed that visual attention is fundamentally controlled by both exogenous (stimulus salience) and endogenous (internal goals and expectations) factors (Corbetta, Kincad, Ollinge, McAvoy, & Shulman, 2000; Corbetta & Shulman, 2002; Corbetta & Shulman, 2011). Emerging evidence suggests that implicit and explicit memories play an important role in attentional control, a process termed memory-guided attention (Chun & Jiang 1998; Moores et al., 2003; Kristjánsson & Campana, 2010; Stokes et al., 2012; Hutchinson & Turk-Browne, 2012; Zhao et al., 2013). For instance, objects semantically related to a target can strongly influence deployment of attention during visual search tasks (Moores et al., 2003). Similarly, previously learned specific location of targets within natural contexts can guide attention to the expected location of targets (Stokes et al., 2012). In addition, repetition of the same target feature, such as color, during visual search can effectively drive spatial attention to the target location (Kristjánsson, 2006; Kristjánsson & Campana, 2010). Moreover, working memory can automatically direct the attention to matching objects in

the environment (Soto, Humphreys, & Rotshtein, 2007). This suggests that attention can be guided by practically all types of memory, including semantic memory, episodic memory, working memory, priming and implicit associative memory.

A common way to establish contexts is through incidental learning of statistical relationships between objects across space. That is, repeated regularities present in the environments tend to be automatically detected and encoded in order to form contexts, and over time, those representations might usefully guide us to the expected location of relevant stimuli. This type of learning usually occurs without previous instruction, without intention of learning, and is not accessible to conscious awareness (Chun & Jiang., 1998; Hutchinson & Turk-Browne, 2012; Goujon, Didierjean, & Thorpe, 2015). Consequently, in some circumstances contexts can be encoded by means of implicit associative learning and can be used to unconsciously guide attention. Perhaps more compelling evidence of how implicit associative memories can guide the deployment of attention comes from the contextual cueing paradigm. In this paradigm, subjects are instructed to search for a target item (e.g., a letter T) embedded in a spatial array of distractor items (e.g,. a set of the letter L). When the target is embedded in a repeated configuration of arrays, the participant's visual search has been shown to be faster compared to a novel configuration of arrays. In the first situation, the distractor items configure a visuo-spatial context that guides attention to the expected location of the target. Interestingly, participants do not explicitly recognize repeated configurations of arrays (Chun & Jiang 1998; Chun & Phelps 1999). Thus, implicit contextual memory can unconsciously and automatically guide visual attention independently of stimulus salience or task rules and goals.

1.3 Neural mechanisms of memory-guided attention

Since attention is a process where some stimuli are processed preferentially over other stimuli, attention necessarily involves the modulation of neural activity in brain regions specialized for perceptual processing, from early

sensory areas to higher-level regions. In the endogenous control of attention, dorsal posterior parietal and frontal cortex (intraparietal sulcus - frontal eye field) influences the magnitude and speed of neural activity in sensory areas (Desimone & Duncan, 1995; Luck, Chelazzi, Hillyard, & Desimone, 1997; Kastner & Ungerleider, 2000; Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005), whereas in exogenous control of attention, early sensory processing automatically recruits the ventral fronto-parietal network (ventral frontal cortex - temporoparietal junction) involved in the bottom-up detection of salient or unexpected events, and redirects attention via connections with the frontal eyes fields (Corbetta & Shulman, 2002). Importantly, it has been suggested that the ventral fronto-parietal attention network is deactivated by the dorsal fronto-parietal attention network to prevent stimulus-driven reorienting during endogenous control of attention. On the contrary, the ventral frontoparietal network acts as a switch of the ongoing top-down control (Corbetta & Shulman, 2002; Corbetta, Patel, & Shulman, 2008). However, in the case of memory-guided attention the neural mechanisms through which memories bias perceptual processing, and how these mechanisms are influenced by top-down or bottom-up processing, are not well understood.

One possibility is that some types of memory might directly influence neural activity involved in sensory processing, resulting in deployment of attention to a memory-related stimulus. In the case of attentional priming, exposure to one stimulus will leave a short-term trace of excited and inhibited neurons in sensory regions. Over time, this trace might facilitate the processing of another stimulus if early and later stimuli share features (Lamme, 2003; Hutchinson & Turk-Browne, 2012). Indeed, is thought that the suppression of activity in subpopulations of visual neurons observed in priming task is an important neural property that likely contributes to select which stimulus is attended to (Desimone, 1996). Similarly, it has been suggested that fMRI BOLD signal deactivations in visual cortex observed in the contextual cueing paradigm reflect more fluent processing of repeated contexts (Westerberg, Miller, Reber, Cohen, & Paller, 2011). Thus, these findings indicate that memory directly influences the sensitivity of neurons in sensory regions to automatically bias perception, particularly, in the case of implicit memories.

An alternative possibility is that memory systems indirectly control perceptual processing through the neural networks specifically dedicated to attention. fMRI studies suggest that, in episodic memory-guided attention, the hippocampus interacts with the dorsal fronto-parietal attention network to bias perceptual processing in visual cortex (Stokes et al., 2012). In addition, it has been reported that explicit memory-guided attention involves functional interactions between the dorsal fronto-parietal attention network and a posterior subnetwork (posterior precuneus, posterior callosal sulcus/mid-cingulate, and lateral intraparietal sulcus) within the cognitive control network typically related to retrieval of explicit memories (Rosen, Stern, Michalka, Devaney, & Somers, 2015). Indeed, new evidence suggests that this subnetwork plays an exclusive role in integrating information retrieved from long term memory for guiding visual attention (Rose, Stern, Devaney, & Somers, 2017). In line with this finding, it has been suggested that the dorsal parietal cortex and the ventral parietal cortex play a role in memory similar to their role in attentional control. According to this view, the hippocampus might interact with the ventral parietal cortex to mediate bottom-up capture of attention by spontaneous and involuntary retrieved contents, while the interaction between (dorsolateral) PFC and dorsal parietal cortex would mediate top-down capture of attention by voluntarily retrieved contents (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008 ; Hutchinson et al., 2009; Ciaramelli, Grady, Levine, Ween, & Moscovitch, 2010). Importantly, if the ventral frontoparietal attention network is recruited to translate spontaneous and involuntary representations into an attentional control signal, this raises the possibility that implicit contextual memory-guided attention must compete for neuronal resources with the dorsal frontoparietal attention network in order to bias attention. Taken together, these findings indicate that both explicit and implicit memory systems may use general attentional networks in order to exert attentional control.

2 SCIENTIFIC AIMS AND HYPOTHESES

2.1 Preliminary evidence suggests that implicit contextual memory-guided attention involves the interaction between brain areas related to the formation of associative memories, including the hippocampus, and the fronto-parietal ventral attention network to provide attentional control signals to the fronto-parietal dorsal attention network. This raises the question how the implicit contextual memory system competes for neural resources typically dedicated to top-down control of attention, and reopens the debate on the participation of the hippocampus in implicit forms of learning. The overall aim of this doctoral thesis was to gain a better understanding of the neurocognitive mechanisms for implementing implicit memory-guided attention. Aims and hypotheses of study 1

Study 1 aims at providing relevant evidence supporting the notion that the hippocampus plays a critical role in implicit learning of contextual information. Automated segmentation of structural MRI is combined with neurobehavioral assessments of implicit contextual memory to test the hypothesis that hippocampal volume would positively predict the magnitude of implicit contextual learning. It is assumed that both, left and right hippocampal volumes positively predict performance in contextual cueing.

2.2 Aims and hypotheses of study 2

Study 2 investigated if dorsolateral prefrontal cortex interferes with implicit contextual memory-guided attention. Continuous theta-burst stimulation (cTBS), electroencephalography (EEG) and neurobehavioral assessment of implicit contextual memory is used to test the hypothesis that transient disruption of DLPFC function would improve implicit memory performance and decrease related low beta-band oscillatory power.

3 EMPIRICAL STUDY 1: THE HIPPOCAMPUS AND IMPLICIT CONTEXTUAL MEMORY-GUIDED ATTENTION

3.1 Abstract

Recent findings highlight the role of Implicit contextual memory for controlling deployment of visual attention. fMRI, pharmacological and neuropsychological studies has implicated the hippocampus in implicit contextual memory-guided attention. However, there is an ongoing debate about whether the hippocampus can support implicit forms of memory. Here I combine automated segmentation of structural MRI with neurobehavioral assessment of implicit contextual memory-guided attention to test the hypothesis that hippocampal volume would predict the magnitude of implicit contextual learning. Forty healthy subjects underwent 3T magnetic resonance imaging brain scanning with subsequent automatic measurement of the total brain, amygdalar and hippocampal volumes. implicit contextual memory-guided attention was measure using the contextual cueing task. I found that both left and right hippocampal volumes positively predicted the magnitude of implicit contextual learning. Larger hippocampal volume was associated with superior implicit contextual memory-guided attention. This study provides compelling evidence that implicit contextual memory-guided attention is hippocampus-dependent.

3.2 Background

Results from numerous studies have suggested that the hippocampus is essential for associative learning. Specifically, it has been reported that the hippocampus is critical for encoding and retrieval of object-context associations. For instance, functional MRI studies have shown that when subjects are encouraged to complete face-name, face-word, item-background scenes, and person-house association's task, the hippocampus is exclusively engaged during encoding of items relationally rather than when they are encoded individually (Henke, Buck, Weber, & Wieser, 1997; Cohen et al., 1999; Giovanello, Verfaellie, & Keane, 2003; Staresina & Davachi, 2008). Additionally,

brain imaging, electrophysiological and neuropsychological studies suggesting that the hippocampus is important to establish associations between objects and their spatial location. It has been reported that the hippocampus exhibits complex patterns of activation during learning of object-location associations (Manelis, Reder, & Hanson, 2011), human hippocampal neurons respond selectively to conjunctions of places, view of landmarks and navigational goals (Ekstrom et al., 2003), and patients with hippocampal damage showed deficits remembering object-location associations (Burgess, Maguire, & O'Keefe, 2002). In addition, recent findings using a Pavlovian fear conditioning in humans support the notion that the hippocampus is critical for contextual encoding. For instance, increased hippocampal activation has been shown during the acquisition of contextual fear conditioning. Similarly, a positive correlation between hippocampal volume and contextual fear conditioning has been reported (Pohlack et al., 2012). Collectively, these studies suggest that one of the most important functions of the hippocampus consist in binding elements with their context in order to form memories.

While there has been general consensus that the hippocampus is critical for encoding and retrieval relational memories, the selective role of the hippocampus in conscious or declarative expressions of relational memories is currently a subject of intense debate (Chun & Phelps, 1999; Manns & Squire, 2001; Park, Quinlan, Thornton, & Reder, 2004; Greene, Gross, Elsinger, & Rao, 2007; Preston & Gabrieli, 2008; Westerberg et al., 2011). Traditional models of hippocampal function emphasize the role of the hippocampus in conscious retrieval of past events (Tulving & Schacter, 1990; Moscovitch, 1992; Squire, 2004). According to those theories the hippocampus exclusively support the conscious recollection of event and facts, while other forms of learning, that does not require conscious or deliberative access, depends on different brain systems (Tulving & Schacter, 1990; Moscovitch, 2008). However, recent evidence indicates that the hippocampus is also involved in the unconscious forms of associative learning (Turk-Browne, Scholl, Chun, & Johnson, 2008; Hannula & Ranganath, 2009; Turk-Browne, Scholl, Johnson, & Chun, 2010), including associative priming and implicit contextual learning (Chun & Phelps, 1999; Hannula & Ranganath, 2009). These findings suggest that the

hippocampus is not only a brain region in which associative representations may be formed, but also support both conscious and unconscious expressions of associative learning (Cohen, Poldrack, & Eichenbaum, 1997; Konkel & Cohen, 2009; Henke, 2010; Ranganath, 2010; Hannula & Greene, 2012).

As discussed earlier, Implicit contextual learning has been extensively studied using the contextual cueing task (Chun & Jiang., 1998). Using this paradigm, Chun & Phelps (1999) observed that subjects with hippocampal damage did not show facilitation in search times compared to controls subjects. Similar results were reported by Park et al. (2004), who injected the GABA A agonist midazolam, a benzodiazepine that induces anterograde amnesia, in normal subjects. In addition, Greene at al. (2007), using functional magnetic resonance imaging (fMRI), found that faster search times for repeated contexts is related to greater activation in the hippocampus. Other studies however have suggested that hippocampal BOLD activity is correlated with explicit recognition of repeated contexts (Preston & Gabrieli, 2008; Westerberg et al., 2011). The source of this discrepancy remain under debate (Greene et al., 2007; Preston & Gabrieli, 2008; Westerberg et al., 2011; Geyer, Baumgartner, Müller, & Pollmann, 2012). Thus, in the absence of contradictory evidence, there is increasing evidence that the hippocampus is critically involved in the implicit contextual memory-guided attention.

While several fMRI studies have identified associations between implicit contextual learning and hippocampal BOLD activity, studies on structural brain correlates of implicit contextual learning are almost inexistent. Here, I use structural MRI to test the hypothesis that hippocampal volume would positively predict contextual cueing performance.

3.3 Materials and methods

3.3.1 Participants

Forty healthy subjects (28 males; mean age 27.23, s.d.2.12, range 21–32 years) participated in the study. They were recruited in schools for ambulance rescue workers located in Southern Germany as part of a longitudinal study

investigating predictors of post-traumatic stress disorder (Pohlack et al. 2011; 2012; 2014; Cacciaglia, Pohlack, Flor, & Nees, 2015; Winkelmann et al., 2016). None of the participants had to be excluded due to mental disorders such as major depressive disorder, current or chronic substance abuse, schizophrenia or borderline personality disorder, as assessed with the German version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997). The Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg approved the study, and we obtained written informed consent from all persons before participation.

3.3.2 Stimuli and design

Each experimental session consisted of a 25-minute test phase in which participants completed a version of the Contextual Cueing task (Chun & Jiang, 1998) implemented and executed in Matlab (Natick, MA, USA). The participants were encouraged to search a target item embedded in a spatial array of distractor items. The target was a T stimulus rotated 90 degrees to the right or to the left. The distractor stimulus was an L shape presented randomly in one of four orientations (0°, 90°, 180°, 270°) with a 10 pixel offset at the line junctions. Each display consisted of 12 items (a single target and 11 distractors) randomly positioned in an invisible 8 × 6 matrix (37.2° × 28.3°). For repeated display, the target appeared in the same location within an invariant configuration of distractors across blocks. For each new display, the distractor configurations were newly generated in each block. Visual stimuli were presented on a gray background in a 17-inch Viewsonic VG710b LCD monitor. The participants were seated 50 cm in front of the computer monitor.

Each trial consisted of the presentation of a 500 ms fixation cross, a display presentation (for a maximum of 6 sec) and a variable duration inter-trial-interval (ITI; range 500–1000 ms). During the display presentation, the participants pressed one of the two buttons (“C” or “M”) on a computer keyboard, corresponding to whether the bottom of the T was pointed to the right or to the left. An example of the trial sequence is shown in Fig. 1. Following one practice

block, each subject performed 20 blocks of the search task. Each block contained 24 intermixed trials of 12 repeated and 12 new displays. There were rest periods of 10 sec between bocks.

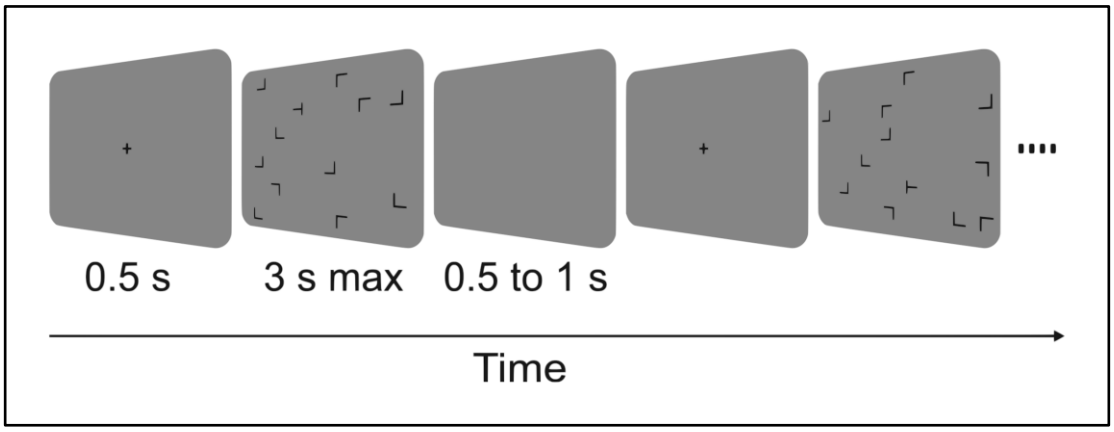

Figure 1. Experimental Paradigm. Each block contained 24 randomly interleaved trials of 12 repeated and 12 new contexts. On each trial, subjects fixated a central cross for 500 ms. After that, a search array was presented for a maximum of 6 sec or until a response was made (subjects indicated whether the bottom of the T was pointed to the right or to the left). A variable duration ITI (500–1000 ms) separated subsequent trials.

3.3.3 Recognition test

After block 20 of the contextual cueing task, the participants were asked if they noticed that certain configurations of the stimuli were repeated from block to block (Chun & Jiang, 1998). Then, an explicit recognition test was carried out to assess awareness of the contextual displays. Importantly, the participants were not informed at the beginning of the experimental session about the recognition test. In this test, the 12 repeated displays used in the experimental session and 12 novel displays were presented in random order (Chun & Jiang, 1998). The participants were informed that certain display configurations were repeated during the experiment and were instructed to indicate whether each display presented was ‘‘repeated’’ or ‘‘new’’ by responding with 1 of 2 keys.

3.3.4 MRI acquisition

Magnetic resonance imaging was performed at the Central Institute of Mental Health in Mannheim with a 3T MAGNETOM Trio whole body scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard 12-channel head coil. T1-weighted high resolution images were acquired with a magnetization-prepared rapid gradient echo (MPRAGE) sequence [TR 2300 ms, TE 2.98 ms, field of view 240 x 256 mm2, 160 sagittal slices, voxel size 1.0 x 1.0 x 1.1 mm3, parallel imaging (GRAPPA) factor 2].

3.3.5 MRI volumetry

Volumetric segmentation of the hippocampus and the amygdala was performed with the Freesurfer 5.0 image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl & Dale, 2000). The processing involves motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white and deep gray matter volumetric structures (including the hippocampus and the amygdala), intensity normalization, tessellation of the gray / white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white matter and gray matter/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Processing was performed on an 8-core UNIX workstation with the Graphics-Processing Unit option enabled. Freesurfer morphometric procedures have been validated against manual segmentation and VBM8 (Grimm et al., 2015) and demonstrate good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006). Finally, right and left hippocampal and amygdalar volumes were calculated in cubic centimeters and then normalized to the estimated total intracranial volume of each individual, also provided by FreeSurfer.

3.3.6 Statistical analyses

For analysis purposes, search reaction times (RTs) of the 20 blocks were grouped into sets of five yielding four epochs and analyzed using two-way repeated measures ANOVA, based on trials performed correctly within [0.5, 6] sec. The independent variables were (1) Context (novel vs. repeated), and (2) Epoch (1 vs. 4). The contextual cueing effect was calculated as the difference in RTs between Old and New arrays collapsed across epochs 3–4 (Chun & Phelps, 1999). Differences in the magnitude of contextual cueing effect were evaluated with Student's t-test. To examine whether participants had explicit recognition of repeated contexts, a paired-sample t test on hits and false alarms for the recognition test was conducted. (Manginelli, Langer, Klose, & Pollmann, 2013). To further address the possibility that explicit recognition of repeated contexts could influence visual search facilitation in the contextual cueing task, the correlation between hit rate and magnitude of contextual cueing effect was calculated (Preston & Gabrieli, 2008; Manginelli et al., 2013). To explore relationships between volumetric and behavioral data, a linear regression analyses were conducted separately for amygdalar and hippocampal volumes. For each regression analysis, contextual cueing performance was entered as dependent variable. To control for possible influences of demographic variables, partial correlations between volumetric and behavioral data were performed, including age, sex and years of education as confounds. For each of the analyses the alpha level was set to 0.05. Data are reported as mean ± SD unless otherwise stated. All analyses and statistical tests were performed in Matlab .

3.4 Results

3.4.1 Search task

Less than 3 % of all trials were omitted from the analyses due to incorrect trials and trials with RT outside of the 0.5 - 6 sec range. Overall accuracy for the new and repeated trials was 99.14 ± 0.9% and 99.34 ± 0.67%, respectively.

Accuracy did not differ by Array Type ($t(39) = 1.67$, $p = 0.102$, $d = 0.26$, Student's t-test).

Consistent with previous findings (Chun & Jiang, 1998; Manelis & Reder, 2012) we found a significant main effect of context (novel vs. repeated), $F(1,39) = 15.41$, $P < 0.001$, $\eta p^2 = 0.29$. indicating that search RTs were faster for repeated than for novel contexts. There was a significant main effect of epoch, $F(1,39) = 169.95$, $p < 0.001$, $\eta p^2 = 0.81$, indicating that search RTs decreased during the task for both types of contexts. In addition, the epoch × context interaction was significant, $F(1,39) = 23.25$, $P < 0.001$, $\eta p^2 = 0.37$, indicating that during the task, search RTs for repeated contexts decreased more than for novel contexts. The magnitude of contextual cueing was significantly greater than zero (0.125 ± 0.129 ms, $t(39) = 6.09$, $p < 0.001$, $d = 0.96$, one sample Student's t-test).

3.4.2 Recognition task

Before the explicit recognition test, participants were asked if they noticed that some displays were repeated during the experiment. None of the participants reported noticing the repeated displays. For the explicit recognition test, the probability that repeated contexts were correctly recognized (hit rate) was 0.32, and this did not differ from the probability that new contexts were misidentified as repeated contexts (false alarm), 0.26, ($t(39) = 1.90$, $p = 0.064$, $d = 0.30$, paired-sample Student's t-test). Furthermore, the hit rate did not correlate with the magnitude of contextual cueing effect ($r = 0.04$, $p = 0.760$). Taken together, there was no evidence of explicit recognition of repeated contexts

3.4.3 Regression analyses

Linear regression analyses conducted on the entire sample revealed that left hippocampal volume significantly predicted contextual cueing performance ($\beta = 0.51$, $t(38) = 3.69$, $p = 0.001$, $r^2 = 0.26$). Right hippocampal volume also significantly predicted contextual cueing performance ($\beta = 0.43$, $t38 = 2.96$, $p = 0.005$, $r^2 = 0.18$), which is illustrated in Fig. 2. As expected we found no significant effects of either left ($\beta = 0.30$, $t38 = 1.97$, $p = 0.056$, $r^2 = 0.09$) or right

(β = -0.00, t38 = -0.02, p = 0.979, r^2 = 0.00) amygdalar volumes in predicting contextual cueing performance).

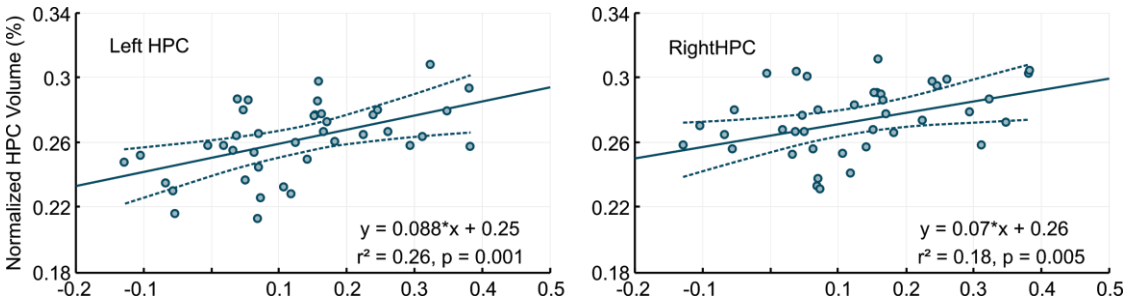

Figure 2. Hippocampal (green circles) volumes significantly predicted contextual cueing performance. Solid lines represent the line of best fit, and dashed lines represent 95% confidence intervals.

3.5 Discussion

Here we investigated the role of hippocampal volume in predicting implicit contextual learning in healthy humans. Consistent with our predictions, contextual cueing scores were positively predicted by hippocampal, but not, amygdalar volumes. Larger hippocampal volume is associated with better performance on implicit contextual memory-guiding attention test.

3.5.1 The hippocampus and the contextual cueing effect

The present data were largely consistent with previous neuropsychological and pharmacological studies on the hippocampus involvement in contextual cueing effect (Chun & Phelps, 1999; Park et al., 2004). Our results also complement previous structural MRI findings that shows a specific link between hippocampal volume and contextual memory performance (Rajah, Kromas, Han, & Pruessner, 2010; Horner et al., 2012; Pohlack et al., 2012). Similarly, these results also are congruent with previous fMRI and PET studies that has shown increased hippocampal activity during the processing of contextual associations (Henke, Buck, Weber, & Wieser, 1997; Cohen et al., 1999; Greene et al., 2007; Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Staresina & Davachi, 2008; Lang

et al., 2009; Manelis & Reder, 2012; Giesbrecht, Sy, & Guerin, 2013; Goldfarb, Chun, & Phelps, 2016). On the contrary, our results are inconsistent with previous evidence showing that patients with hippocampal damage did not exhibit facilitation in search times for repeated contexts (Manns & Squire, 2001).

3.5.2 The hippocampus and the unconscious memory

In agreement with previous reports our results indicating that the facilitation for repeated context did not depends on explicit recognition (Chun & Phelps, 1999; Johnson, Woodman, Braun & Luck, 2007). Our results are consistent with previous studies showing that the hippocampus participate in some types of implicit learning (Hannula & Ranganath, 2009; Turk-Browne et al., 2008, Turk-Browne et al., 2010) and support the view that the hippocampus is not only responsible for encoding and retrieval of contextual information, but also that this processes may done in the absence of awareness (Cohen et al., 1997; Konkel & Cohen, 2009; Reder, Park, & Kieffaber, 2009: Henke, 2010; Hannula & Ranganath, 2009; Hannula & Greene, 2012).

Considered together, these results are consistent with the relational memory theory (Eichenbaum, Otto, & Cohen, 1994). According to this theory the hippocampus is critical for forming associations among items in events while the parahippocampal region are involved in the memory for individual items. Contrary to the idea that the hippocampus plays a selective role in conscious memory (Squire et al., 2004), an extension of the relational memory theory (Cohen et al., 1997; Ryan & Cohen, 2003; Moses & Ryan, 2006; Moscovitch, 2008), suggest that the hippocampus can support relational memory in absence of consciousness and that the conscious awareness of encoded and retrieved content is determinate by the interaction of the hippocampus with other structures (e.g. prefrontal and parietal regions). Therefore, our findings provide compelling evidence that the hippocampus play only an indirect role in conscious memory.

4 EMPIRICAL STUDY 2: DLPFC-MEDIATED TOP-DOWN COGNITIVE CONTROL AND IMPLICIT CONTEXTUAL MEMORY-GUIDED ATTENTION.

4.1 Abstract

Multiples studies have demonstrated that the dorsolateral prefrontal cortex (DLPFC) plays an important role in top-down cognitive control over intentional and deliberate behavior. However, recent findings revealed that DLPFC mediated top-down control could interfere with implicit forms of learning. Moreover, behavioral findings have suggested that top-down cognitive control can interfere with implicit contextual memory-guided attention. I used continuous theta-burst stimulation (cTBS), EEG and neurobehavioral assessment of implicit contextual memory to test the hypothesis that transiently disruption of the left DLPFC function would improve implicit memory performance and decrease underlying low beta-band oscillatory power. I found that cTBS applied over the left DLPFC improved significantly performance during implicit contextual learning. We also observed that beta-band (13-19 Hz) oscillatory power was reduced at fronto-central channels around 140 to 370 ms after visual stimulus onset in cTBS over DLPFC compared with cTBS over Vertex. Taken together, our results provide evidence that the DLPFC-mediated top-down control interferes with implicit contextual memory-guided attention and support the notion that beta-band oscillatory activity promote DLPFC mediated top-down control.

4.2 Background

Implementation of goal-directed behaviors requires of a set of cognitive functions such as selective attention, inhibitory control, error monitoring, planing, or working memory, to limit attention to relevant information and suppress irrelevant distraction. Process generally termed executive cognitive control (Cole & Schneider, 2007; Amer, Campbell, & Hasher, 2016). Findings

from several studies indicate that executive cognitive control involve the coordination of large-scale brain networks through the synchronization of neural oscillations. Particularly, there is evidence that low-beta oscillations play a critical role in top-down cognitive control (Engel, Fries, & Singer, 2001; Engel & Fries, 2010; Helfrich & Knight, 2016). Although enhanced cognitive control is useful to goal-directed behavior, there is evidence that that top-down cognitive control interfere with implicit learning (Kübler, Dixon, & Garavan, 2006; de Manzano et al., 2012, Lee et al., 2013).

Multiple studies have demonstrated that cognitive control stem from a set of fronto-parietal regions (anterior cingulate cortex/pre-supplementary motor area, DLPFC, inferior frontal junction, anterior insular cortex, dorsal pre-motor cortex, and posterior parietal cortex), often called cognitive control network (Cole & Schneider 2007). Importantly, the DLPFC, a region within the cognitive control network, has been specifically involved in the exerting top-down cognitive control over intentional and deliberate behavior by suppressing automatic behaviors (Kübler et al. 2006; de Manzano & Ullén, 2012). Therefore, it has been suggested that reducing cognitive control facilitates automatic behaviors and implicit forms of learning. Compelling evidence for the DLPFC role in implicit learning comes from a recent transcranial magnetic stimulation (TMS) study, which shows that inhibition of the DLPFC function improved implicit recognition, suggesting that DLPFC-mediated explicit memory processes interfere with implicit recognition memory (Lee, Blumenfeld, & D'Esposito, 2013). Moreover, DLPFC inhibition and concomitant decrease in conscious self-monitoring and focused attention has been implicated in promoting implicit spontaneous associations (Limb & Braun, 2008; Liu et al., 2012). In line with these findings, evidence from EEG studies supports an important role of beta-band activity (BBA) in endogenous top-down cognitive control (Engel & Fries, 2010). Interestingly, several studies indicate that task-related BBA predominates in paradigms that involve high cognitive control, whereas settings that require little or no cognitive control decrease BBA (Engel et al., 2001; Okazaki, Kanek, Yumoto, & Arima, 2008; Iversen, Repp, & Patel, 2009; Engel & Fries 2010). Thus, reducing BBA could reflect low endogenous cognitive control.

Further support for top-down cognitive control interference with implicit memory processes comes from the observation that implicit contextual learning is variable among individuals. There is evidence that between 30% to 40% of individuals do not show contextual cueing effect (Lleras & von Mühlenen, 2004; Schlagbaue, Müller, Zehetleitner, & Geyer, 2012). It has been suggested that different cognitive search strategies could be the reason for the performance variation in contextual cueing. Lleras & von Mühlenen (2004) found that when participants were instructed to search actively for the target, by deliberately shifting their attention, the contextual cueing effect was disrupted. On the contrary, the contextual cueing effect was facilitated when participants adopt a passive search strategy. These findings do suggest that voluntary cognitive control can interfere with implicit contextual memory-guided attention.

Here, I addressed the question whether DLPFC-mediated top-down control interferes with implicit contextual memory-guided attention. To examine this question, I used continuous theta-burst stimulation (cTBS) to transiently disrupt the function of DLPFC and measured the resulting effects on behavioral and oscillatory responses in an implicit contextual memory task. I hypothesized that disruption of the left DLPFC function by cTBS would improve implicit memory performance and decrease task-related beta-band oscillatory activity.

4.3 Materials and methods

4.3.1 Participants

Twenty-one healthy subjects (11 females; range 19-33 years) with no history of neurological or mental disorder participated in the study. Right-handedness was verified using the Edinburgh Handedness Inventory (Oldfield, 1971). The Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg approved the study and written informed consent was obtained from all persons before participation.

4.3.2 Experimental procedure

Participants initially underwent magnetic resonance imaging (MRI) in order to acquire an anatomical scan, which was used to individually define the DLPFC target. Then, the participants were invited to the laboratory for two separate sessions, both consisting of concurrent TMS and EEG recordings (1-week interval between the two sessions). In the one session, the participants received cTBS over the DLPFC, and in the other session they received cTBS over the Vertex. The order of stimulation sites (i.e. DLPFC versus vertex) was counterbalanced across participants. Immediately after cTBS administration, the participants completed a version of the contextual cueing task (Chun and Jiang, 1998). Finally, an explicit recognition test was carried out to assess awareness of the contextual displays.

4.3.3 Stimuli and design

Repeated from above in the contextual cueing task, the subjects were encouraged to search a target item embedded in a spatial array of distractor items. The target was a T stimulus rotated 90 degrees to the right or to the left. The distractor stimuli were L-shapes presented randomly in one of four orientations (0°, 90°, 180°, 270°). Each display consisted of 12 items (a single target and 11 distractors) randomly positioned in an invisible 8 × 6 matrix (37.2° × 28.3°). For repeated displays, the target appeared in the same location within an invariant configuration of distractors across blocks. For new displays, the distractor configurations were newly generated in each block. Visual stimuli were presented on a gray background in a 17-inch Viewsonic VG710b LCD monitor. Participants were seated 50 cm in front of the computer monitor. Each trial consisted of a fixation cross presented during 0.5 sec, followed by a display presentation (for a maximum of 3 sec). This was then followed by a new gray background screen with variable duration intertrial-interval (ITI; range 0.5 – 1 sec) preceding the next trial. During the display presentation, the subjects pressed one of the two buttons (“C” or “M”) on a computer keyboard, corresponding to whether the bottom of the T was pointed to the right or to the

left. An example of the trial sequence is shown in Fig. 1. Each subject performed 20 blocks (480 trials) of the search task with each block containing 24 intermixed trials of 12 new and 12 repeated displays. There were rest periods of 10 sec between blocks.

After block 20, the volunteers participated in an explicit recognition test in order to assess awareness of the contextual displays (Chun and Jiang, 1998). In this test, the 12 repeated displays used in the experimental session and 12 new displays were presented in random order. Participants were instructed to indicate whether each display presented was ‘‘repeated’’ or ‘‘new’’ by responding with one of two response buttons. The task was implemented in MATLAB (Math-Works, Natick, MA, USA) using the open-source Psychophysics toolbox 3 (Brainard, 1997).

4.3.4 Magnetic Resonance Imaging

All participants were examined in a 3T MAGNETOM Trio whole body scanner (Siemens Medical Solutions, Erlangen, Germany) at the Central Institute of Mental Health in Mannheim with a equipped with a standard 12-channel head coil. T1-weighted high resolution images were acquired with a magnetization-prepared rapid gradient echo (MPRAGE) sequence [TR 2300 ms, TE 2.98 ms, field of view 240 x 256 mm2, 160 sagittal slices, voxel size 1.0 x 1.0 x 1.0 mm3, parallel imaging (GRAPPA) factor 2].

4.3.5 Determination of the TMS Sites from Magnetic Resonance Images

The location of the DLPFC target was chosen based on a previous study showing improvement in recognition accuracy after TMS applied over DLPFC using standard-space coordinates from the Montreal Neurological Institute (MNI) brain (i.e. -43, 35, 30; Lee et al., 2013), Fig. 3. For each participant, the DLPFC target coordinates were transformed into the participant’s native MRI space with the reversed MNI152 template-to-native transformation matrix employing FSL software. The individually-defined DLPFC coordinates were then used as a center to draw a 5mm-radius region-of-interest, which was the TMS target. In addition, we also applied TMS over the vertex to control for

nonspecific effects of TMS, such as acoustic and somatosensory artifacts. The vertex was defined anatomically by the intersection between a sagittal line form the nasion to the inion and a coronal line from the tragus of both ears.

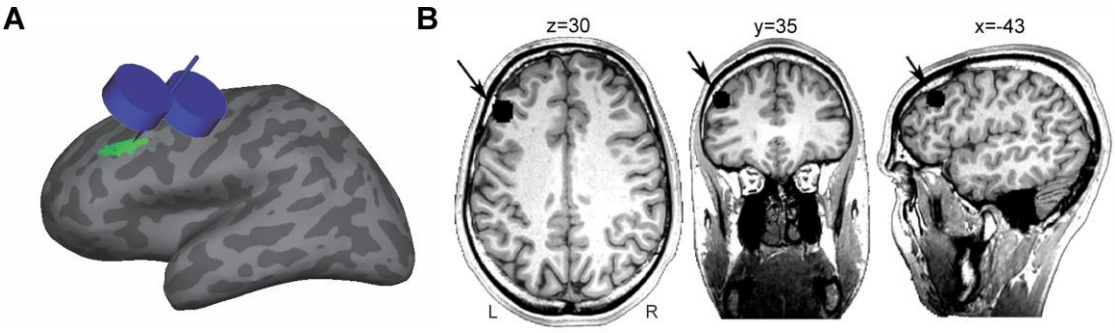

Figure 3. Definition of the dorsolateral prefrontal cortex (DLPFC) used as a TMS target. The DLPFC target was defined by the coordinates (-43, 35, 30) in MNI152 space and transformed into each participant's native space for frameless stereotaxy. The arrows indicate the location of the DLPFC target shown on a template brain in MNI152 space.

4.3.6 Transcranial magnetic stimulation

For each participant, we determined the resting motor threshold (MT), which is defined as the lowest stimulus intensity capable of eliciting a motor-evoked potential MEP > 50 μV in the relaxed abductor pollicis brevis (APB) in 5 of 10 consecutive trials at intervals > 5 s (Rothwell et al., 1999). TMS was delivered using a 75mm winding diameter figure-of-eight coil (MCF-B65) and a MagProX100 stimulator (MagProX100, MagVenture, Denmark).

In order to guide the coil over the DLPFC location for each participant, we used a neuronavigation procedure, which was performed using the Brainsight system (Rogue Research, Canada) equipped with an infrared camera for online subject tracking and coil positioning (Polaris Spectra, NDI, Canada).

After the motor threshold procedure, repetitive TMS was carried out using a continuous theta burst stimulation protocol (cTBS) consisting of three pulses at 50 Hz repeated at a frequency of 5 Hz. Thus, a total of 600 pulses were delivered over a period of 40 s preceding the start of the task (Huang et al.,

2005). The stimulus intensities were set at 90% of each participant's resting motor threshold. TMS was applied with the coil held tangentially to the skull, with the handle pointing backward and laterally at a 45-degree angle away from the midline. TMS sessions were performed according to the published safety guidelines (Wassermann et al., 1996; Rossi et al., 2009).

4.3.7 EEG acquisition

The EEG was recorded from 30 scalp electrodes mounted in a BrainCap TMS (BrainProducts, Munich, Germany) at the following sites (M-22 Equidistant 32-Channel-Arrangement): Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, Fz, Cz, Pz, Iz, FC1, FC2, CP1, CP2, FC5, FC6, CP5, CP6, TP9, TP10. Blinks and eye movements were monitored by using two pairs of bipolar electrodes placed approximately 1 cm lateral to the left and right external canthi (HEOG) and above and below the subject's right eye (VEOG). Electrode impedances were kept below 10 kΩ using conduction gel. AFz and FCz served as ground and reference electrode for online recording. Data were band-pass filtered from 0.016 to 250 Hz during recording and digitized with a sampling rate of 1000 Hz using BrainAmp amplifiers (BrainProducts, Munich, Germany).

4.3.8 Analysis of behavioral data

Accuracy and search reaction times (RTs) for correct trials were grouped into sets of four yielding five epochs in order to increase the power of the statistical analyses (Chun and Jiang, 1998).

For accuracy and RTs, we carried out a three-way ANOVAs using contexts (new versus repeated), epochs (1-5) and cTBS sites (DLPFC versus vertex) as factors.

In addition, for RTs, we performed separate two-way repeated measures ANOVAs for each cTBS site (i.e., DLPFC, vertex), the factors were contexts (new versus repeated) and epochs (1-5).

The contextual cueing effect was calculated using the difference in RTs between new and repeated contexts (for each epoch). These values were then

entered in a two-way repeated measures ANOVA with Context (new versus repeated) and epochs (1-5) as factors.

We also assessed interindividual variation in implicit contextual learning. For this purpose, the contextual cueing effect was calculated as the difference in RTs between new and repeated contexts collapsed across epochs 2-5.

Finally, for the explicit recognition test, a paired-sample t test on hits and false alarms was conducted.

For all analyses the alpha level was set to 0.05. Data are reported as mean ± SD unless stated otherwise.

4.3.9 EEG data analysis

Analysis of the EEG data was performed using EEGLAB 4.51 (Delorme and Makeig, 2004), Fieldtrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) and custom scripts on the MATLAB 8.5 platform (Math-Works, Natick, MA, USA). Data were low-pass filtered at 120 Hz and high-pass filtered at 0.2 Hz (FIR filter) and downsampled to 500 Hz. For further analysis, epochs from -500 ms before to 800 ms after stimulus onset, were extracted. Trials containing non-stereotyped artefacts (e.g., cable movement, swallowing) and amplitudes of more than ±100 μV were removed. This led to the rejection of 19.3 % trials. Finally, to reduce the remaining artefacts (e.g., eyeblinks, horizontal eye movements, and electrocardiographic activity) an extended infomax independent component analysis (ICA) was applied on the data using a weight change <10−6 as stop criterion (Bell & Sejnowski, 1995), and components that reflected signal artefacts were removed from the EEG data. Artefact components were identified using visual inspection of their topography, power spectrum, and temporal dynamics.

Spectral changes in total oscillatory activity (phase-locked and non- phase-locked to stimulus onset) were analyzed using the ‘multitaper method’ (Mitra & Pesaran, 1999) based on discrete prolate spheroidal slepian sequences (Slepian, 1978). Time-frequency representations (TFRs) were computed using a sliding window (ΔT= 250 ms), applied in steps of 10 ms (-370 ms before to 370 ms after stimulus onset), with a frequency smoothing (Δf= ±4 Hz; 4–30 Hz),

resulting in one taper applied to the sliding window. Then, the Fourier transforms of the tapered time windows were calculated. To estimate evoked oscillatory activity, we first averaged across trials for each condition before computing the spectral estimates. To estimate induced oscillatory activity, we first subtracted from each individual trial the evoked part before computing the spectral estimates. All the presented data represent baseline-normalized (-200 to -100 ms) relative changes in power:

$$Pow(t,f)_{normalized} = (Pow(t, f) - Pow(f)_{baseline}) / Pow(f)_{baseline}.$$

For statistical testing of differences in spectral power (repeated versus new context; cTBS DLPFC versus cTBS vertex), we used a cluster-based permutation test (Maris & Oostenveld, 2007). In short, a simple dependent-samples t-test was calculated at each time point, frequency bin, and channel of the two experimental conditions. Then, all adjacent samples with t-values exceeding a preset significance level (5%) were grouped into clusters. The sum of t-values from the cluster with the maximum sum was then used as the test statistic. Next, a null distribution of cluster-level t-statistics was created by randomly shuffling the data across the two conditions using 1000 permutations. Cluster values greater or smaller than the 97.5th percentile ($P < 0.025$) were considered to be significant. To identify time windows and the frequency range of significant relative power differences, we first compared the spectral power between the repeated versus new context and then between cTBS DLPFC versus cTBS vertex within the 4 to 100 Hz frequency band and the post-stimulus interval from 0 to 370 ms, using a sliding-time window fieldtrip cluster statistic (Staudigl & Hanslmayr, 2013; Waldhauser, Braun, & Hanslmayr, 2016). Then, significant time-frequency windows were subjected to another cluster-based permutation test to identify significant locations. This resulted in a beta frequency range of interest between 13 to 19 Hz and 140 to 370 ms. To test for a possible interaction between context and cTBS sites, we first calculated the differences between (1) repeated and new contexts in cTBS DLPFC and (2) repeated and new contexts in cTBS vertex. Next, we contrasted these differences using a cluster-based permutation test.

4.4 Results

4.4.1 Search task

Participants were highly accurate (98.3%). Accuracy did not differ between contexts (new vs.versus repeated), ($F(1,20) = 0.19$, $P = 0.66$), epochs (1-5), ($F(4,80) = 1.07$, $P = 0.37$), or cTBS sites (DLPFC versus vertex), ($F(1,20) = 0.04$, $P = 0.84$), and there was no significant interaction between contexts, epochs and cTBS sites ($F(4,80) = 2.00$, $P = 0.10$). In addition, no significant interaction was found between contexts and epochs, $F(4,80) = 0.88$, $P = 0.47$, contexts and cTBS sites, $F(1,20) = 3.10$, $P = 0.09$, or epochs and cTBS sites, $F(4,80) = 0.01$, $P = 0.99$.

For RTs, we found a significant three-way interaction between contexts (new versus repeated), epochs (1-5), and cTBS sites (DLPFC versus vertex), $F(4,80) = 3.48$, $P < 0.01$. To establish the source of these interactions, the data from each cTBS site were separately analyzed (Fig. 4A). For cTBS DLPFC, the main effect of contexts (new versus repeated) was significant, $F(1,20) = 75.28$, $P < 0.001$, indicating that search RTs were faster for repeated than for new contexts. There was a significant main effect of epochs (1-5), $F(4,80) = 43.94$, $P < 0.0001$, indicating that search RTs decreased during the task. A significant contexts by epochs interaction, $F(4,80) = 8.70$, $P < 0.0001$, showed that for cTBS DLPFC, search RTs for repeated contexts decreased more than for new contexts. Post hoc analyses using Bonferroni's correction ($P < 0.05$) indicated that for cTBS DLPFC, the mean RT was significantly faster for repeated than for new contexts only during epochs 2-5.

For cTBS vertex there was a significant main effect of contexts (new versus repeated), $F(1,20) = 18.81$, $P < 0.001$, indicating that search RTs were faster for repeated than for new contexts. There was a significant main effect of epochs (1-5), $F(4,80) = 52.51$, $P < 0.0001$, showing that search RTs decreased during the task. No significant interaction was found between contexts and epochs for cTBS Vertex, $F(4,80) = 0.55$, $P = 0.69$.

The analysis of magnitude of the contextual learning (contextual cueing effect) as a function of cTBS sites (DLPFC versus vertex) and epochs (1-5), Fig. 4B,

revealed that there was a significant main effect of cTBS sites (DLPFC versus Vertex), $F(1,20) = 23.04$, $P < 0.001$, indicating that contextual learning performance differed between DLPFC and vertex cTBS. Additionally, a significant main effect of epochs (1-5) was found $F(4,80) = 7.89$, $P < 0.001$, showing that contextual learning increased during the task for both cTBS sites. There was a significant interaction between the effects of cTBS sites and epochs for implicit contextual learning performance, $F(4,80) = 3.48$, $P < 0.05$, indicating that cTBS DLPFC effect compared to cTBS vertex was different during the task. Post hoc analyses using Bonferroni's correction ($P < 0.05$) revealed that the mean of the contextual learning performance for cTBS DLPFC was significantly higher than cTBS vertex only during epochs 2-5. Importantly, 100% and 72% of the participants showed the contextual cueing effect during cTBS DLPFC and cTBS Vertex, respectively (contextual cueing effect estimated across epochs 2-5).

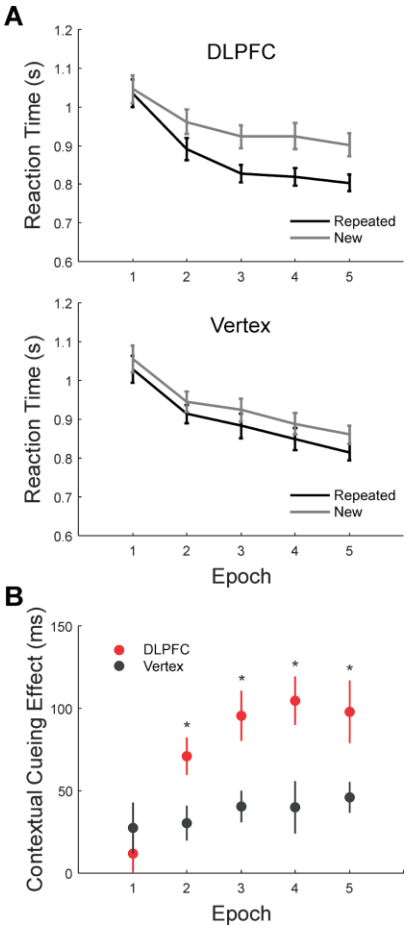

Figure 4. Behavioral performance in the contextual cueing task. A) Mean reaction times (with standard error of the mean) for cTBS DLPFC (top) or cTBS

vVertex (bottom) as a function of epoch and context. B) The contextual-cueing effect (with standard error of the mean) as a function of cTBS site and epoch .

4.4.2 Recognition task

Before the explicit recognition test, participants were asked if they noticed that some displays were repeated during the experiment. None of the participants reported noticing the repeated displays. For the explicit recognition test, participants recognized repeated contexts as repeated on 27% (hit rate) of the cTBS DLPFC trials and this did not differ from the percentage of new contexts misidentified as repeated contexts (false alarm), 27% ($P = 0.28$, Student's t-test). For the cTBS vertex condition, the hit rate was 27% and this did not differ from the false alarm rate, 30% ($P = 0.57$, Student's t-test). The hit rate and the false alarm rate did not significantly differ between the two cTBS conditions ($P = 1.00$, and $P = 0.20$, Student's t-test, respectively), Taken together, there was no evidence of explicit recognition of repeated contexts, in both conditions.

4.4.3 Total oscillatory activity

cTBS DLPFC significantly decreased task-related beta-band activity compared to cTBS vertex, in a frequency range of 13-19 Hz and a time window from 140 to 370 ms after stimulus onset (Fig. 5A right, B). This effect was restricted to the F3, F4 and P3 channels (cluster-corrected permutation test, $P = 0.018$, Fig. 5B). A time-frequency analysis of significant channels is shown in Fig. 5C. There was no significant difference in task-related oscillatory activity between repeated and new contexts. The sliding windows analysis did not show significant differences between the repeated and the new contexts in any time window or frequency range (Fig. 5A left). Finally, permutation testing did not show an interaction between cTBS sites and contexts in the beta-band (13-19 Hz, 140-370 ms, cluster-corrected permutation test, $P > 0.1$). This suggests that cTBS reduced the task-related beta-band oscillatory power independently of the contexts.

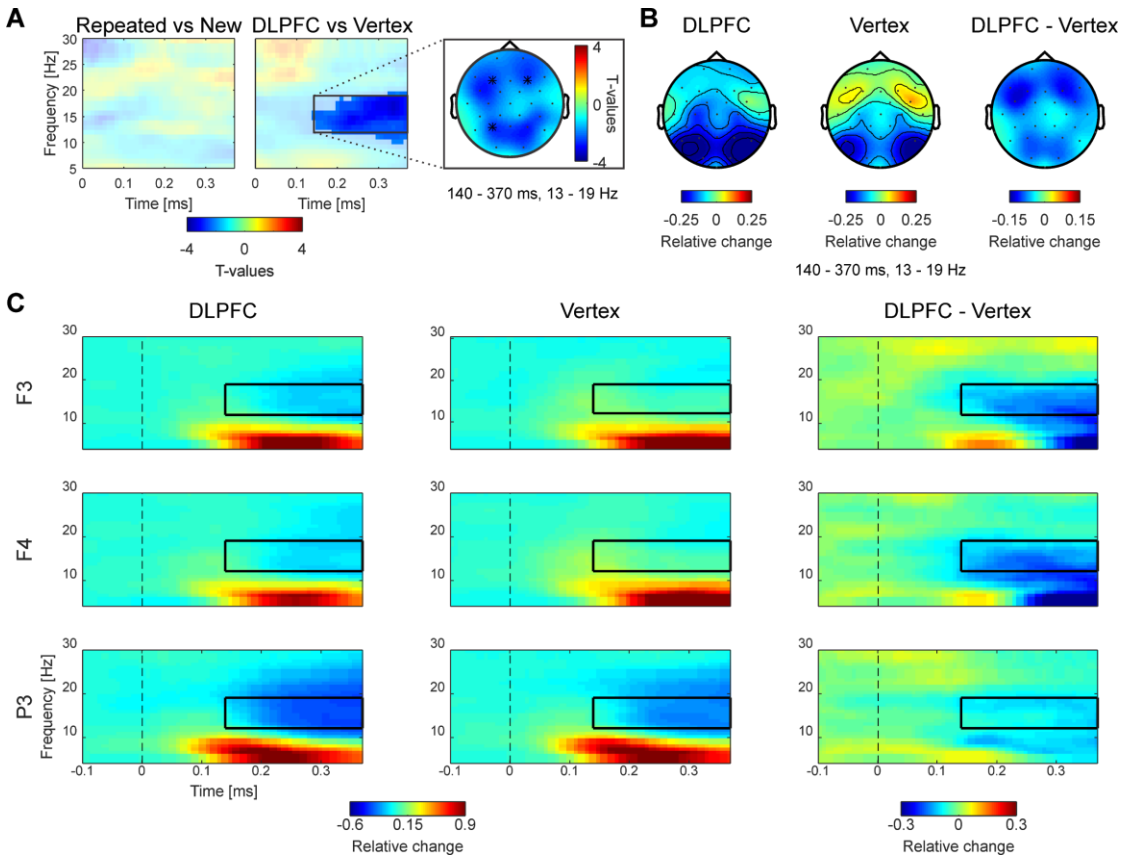

Figure 5. Analysis of total oscillatory activity. (A) Results from the two-step time-frequency analysis. Time-frequency window (13-19 Hz, 140-370 ms, dashed box) for DLPFC versus vertex contrast but not for the repeated versus new context contrast was identified by sliding window analyses, and survived a cluster-based permutation test. On the right, the topography of the results from the cluster-based dependent t-test randomization procedure over the window of interest (13-19 Hz, 140-370 ms) for the DLPFC versus vVertex contrast is depicted (pcorr < 0.05). Channels showing a significant interaction are highlighted. (B) Topographic distribution of significant post-stimulus beta-band activity (13-19 Hz, 140-370 ms). Topographies are depicted for DLPFC TMS, vertex TMS, and their differential activity (cTBS DLPFC versus cTBS vVertex). (C) Time–frequency representations of total oscillatory activity at F3, F4 and P3 channels. Time-frequency representations are depicted for cTBS DLPFC, cTBS vVertex, and their differential activity (i.e., cTBS DLPFC versus cTBS vertex). Vertical dashed lines indicates stimulus onset.

4.4.4 Induced oscillatory activity

I investigated induced oscillatory activity to test if the main effect of cTBS on task-related beta-band activity related to the modulation of non-phase-locked oscillatory responses. As for the total oscillatory beta analyses, the induced beta-band activity analyses revealed that F3, F4 and P3 electrodes showed a significant decrease in beta band power (13-19 Hz, 140-370 ms) in the DLPFC cTBS compared to the vertex cTBS (cluster-corrected permutation test, P = 0.022), Fig. 6A, B). A time-frequency analysis on significant channels is shown in Fig. 6C. Finally, we conducted cluster-based statistical analyses to evaluate the interaction between cTBS sites and contexts in the beta-band (13-19 Hz, 140-370 ms). No significant interaction effect was found in the beta frequency range (cluster-corrected permutation test, P > 0.10).

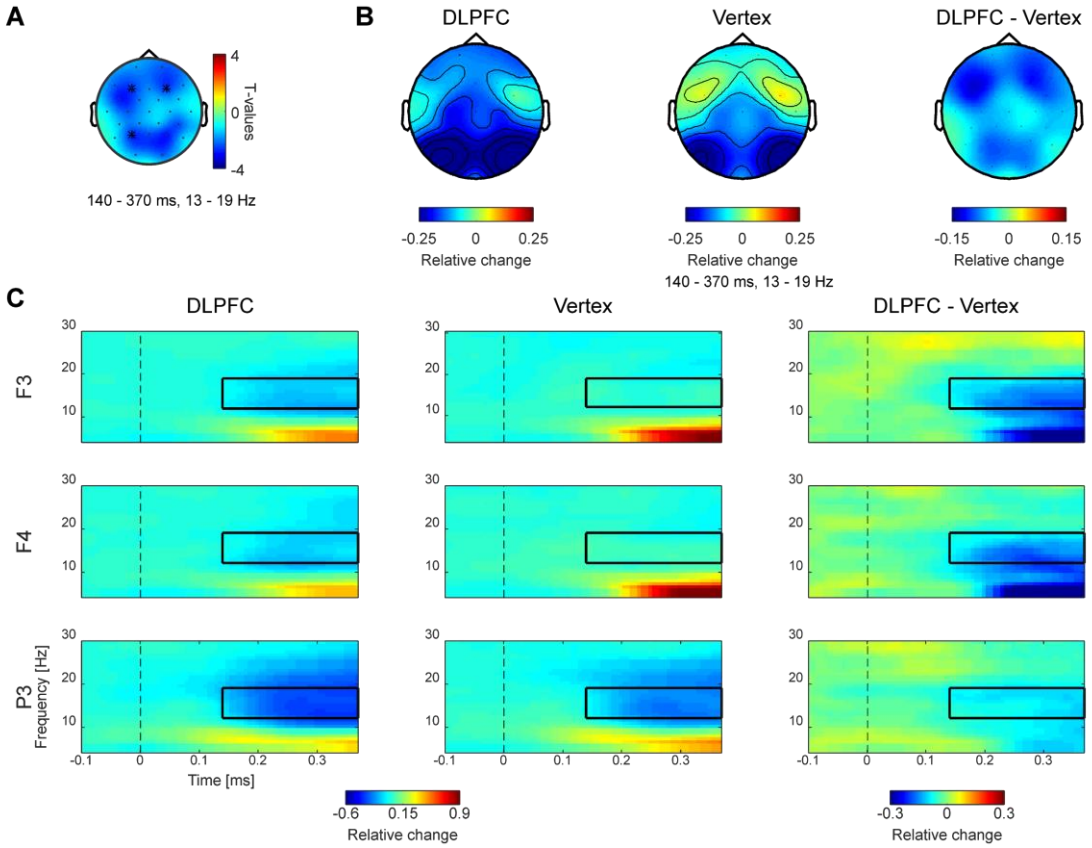

Figure 6. Analysis of the induced oscillatory activity. (A) The topography of the results from the cluster-based dependent t-test randomization procedure over the window of interest (13-19 Hz, 140-370 ms) for the cTBS DLPFC versus cTBS vertex contrast is depicted (pcorr < 0.05). Channels showing a significant

interaction are highlighted. (B) Topographic distribution of significant post-stimulus beta-band activity (13-19 Hz, 140-370 ms). Topographies are depicted for cTBS DLPFC, cTBS vertex, and their differential activity (cTBS DLPFC versus cTBS vertex). (C) Time–frequency representations of induced oscillatory activity at F3, F4 and P3 channels. Time-frequency representations are depicted for cTBS DLPFC, cTBS vertex, and their differential activity (cTBS DLPFC versus cTBS vertex). Vertical dashed lines indicates stimulus onset

4.5 Discussion

Although enhanced cognitive control improves goal-directed behavior, there is evidence that reduced cognitive control is beneficial for automatic behaviors and implicit forms of learning. The DLPFC is thought to exert top-down cognitive control by means of inhibition of automatic (implicit) processes. Thus, DLPFC deactivation should significantly facilitate implicit learning. In the present study, we investigated whether reduced cognitive control through DLPFC disruption could enhance implicit contextual memory-guided attention. In addition, we investigated whether DLPFC disruption and concomitant reduced cognitive control would be reflected in decreased beta-band oscillatory activity. As predicted, I found that cTBS applied to the DLPFC led to a robust increase in implicit contextual memory performance compared with cTBS applied to the vertex as a control condition. Moreover, cTBS over the DLPFC significantly decreased beta-band oscillatory activity (13-19 Hz, 140-370 ms) at fronto-central channels.

4.5.1 TMS and the contextual cueing task

Our behavioral results were consistent with previous findings (Chun & Jiang, 1998; Chun & Phelps, 1999; Johnson et al., 2007; Manelis & Reder, 2012). In the visual search task, participants were highly accurate and showed a general RT facilitation for repeated contexts in both cTBS conditions. Importantly, as an earlier experiments our results of the recognition task indicated that repetition facilitation effect occurs implicitly (Chun & Jiang, 1998; Chun & Jiang, 2003).

Our results show that disruption of DLPFC processing using cTBS enhanced implicit contextual memory. This result provided a first link between DLPFC and implicit contextual memory-guided attention. The observed improvement is in line with previous observations that DLPFC disruption by cTBS facilitates implicit recognition (Lee et al., 2013). On a more general level, our finding is consistent with previous findings suggesting that disengagement of top-down cognitive control through DLPFC deactivation exerts a facilitative effect on implicit processes (Limb & Braun 2008; Liu et al., 2012; Amer et al., 2016). Thus, our TMS results support the notion of DLPFC involvement in top-down cognitive control through suppression of automatic (implicit) processes (Kübler et al., 2006; de Manzano & Ullén, 2012), and provide first causal evidence for the interfering role of DLPFC on implicit contextual learning .

In accordance with previous studies investigating the effects of the duration of cTBS on cortical inhibition, we observed that implicit contextual learning was significantly higher for cTBS DLPFC than vertex cTBS during epochs 2-5. Previous observations showed that cTBS delivered over a period of 40 s reduced brain activity few minutes after stimulation and for up to one hour, with a maximum effect at 15 to 40 min after cTBS (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Thus, the enhanced performance we report here may reflect sufficient cortical inhibition since the beginning of epoch 2 (~8 min after cTBS) until the end of the task, suggesting that the acquisition of implicit contextual memory can happen fast, but top-down cognitive control delays the expression of implicit memory when this task is applied in normal conditions.

In line with previous studies on inter-individual variation in implicit contextual learning (Lleras & von Mühlenen, 2004; Schlagbauer et al., 2012), our results show that in the cTBS vertex condition 72% of the individuals showed the contextual cueing effect. On the contrary, in the cTBS DLPFC condition 100% of the subjects exhibited the contextual cueing effect. This observation supports the notion that inter-individual variation in contextual cueing performance could be explained by the degree of pressure on the attentional system exerted by voluntary cognitive control. High cognitive control (e. g., an active search strategy) through DLPFC participation competes for attentional resources dedicated for processing repeated contexts, abolishing the contextual cueing

effect (Schlagbauer et al. 2012). Similar results were found when a spatial working memory task was combined with the contextual cueing task. In this case, working memory load took away attentional resources reducing implicit contextual learning (Manginelli, Geringswald, & Pollmann, 2012; Annac et al, 2013). Importantly, working memory processing is supported by DLPFC (Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997; Smith, Jonides, Marshuetz, & Koeppe, 1998). We assume that that top-down cognitive control might narrow the focus of attention on target information, and a main part of contextual information remains excluded of both the encoding and retrieval processes. Therefore, reduced cognitive control through DLPFC disruption may have boosted implicit learning by broadening the scope of attention. This mechanism could not only facilitate implicit memory encoding but also later access. Similar mechanisms haves been proposed to explain the facilitatory effect of reduced cognitive control on creativity and problem solving (Amer et al., 2016).

4.5.2 TMS and beta-band activity

I found that task-related beta-band activity (13-19 Hz, 140-370 ms) at fronto-central channels was reduced in cTBS DLPFC compared with cTBS vertex. Our finding is in agreement with a previous study that investigated the after-effect of rTMS over DLPFC on oscillatory responses in healthy subjects. Woźniak-Kwaśniewska et al., (2014) observed that low beta-band oscillatory responses (14-22 Hz) at frontal electrodes decreased after cTBS over the DLPFC. Since beta and gamma oscillations are related to activity of fast-spiking inhibitory interneurons (Cardin et al., 2009), decreased beta-band activity could be interpreted as an indicator of reduced cortical inhibition. Thus, the reduced beta-band activity we reported here may reflect reduced top-down signaling mechanism and consequent diminution of the capacity to produce neural ensemble synchrony necessary to enable voluntary cognitive control.

Several studies indicated that beta-band activity plays an important role in top-down cognitive control. Beta-band synchronization between frontal and parietal areas was observed during attentional top-down processing but not during

bottom-up processing (Buschman & Miller, 2007). In addition, prominent phase synchronization in the beta-band range between frontal and parietal areas was reported during endogenously driven choices in comparison to stimulus driven choices (Pesaran, Nelson, & Andersen, 2008). This suggests that beta-band activity is prominent in settings that involve a strong top-down cognitive control, whereas reduced beta-band activity is more related to tasks that involve exogenous, bottom-up processing (Engel & Fries, 2010). In the light of the above findings, we suggest that the decreased beta-band oscillatory power observed here may be indicative of reduced TMS-induced top-down cognitive control. Therefore, the facilitatory effect of TMS DLPFC on implicit contextual learning could be the result of the suppression of top-down, endogenous processing and concomitant speeding of bottom-up stimulus-driven processing, necessary for encoding and recovering implicit memories. Importantly, our results showed that cTBS reduced the beta-band oscillatory power independently of the contexts, suggesting that it exclusively reflects a top-down cognitive control mechanism but not implicit memory processes.

5 General Discussion

5.1 Main findings

In this dissertation a number of open questions about the role of the hippocampus and DLPFC in implicit contextual memory-guided attention were addressed. Through combination of automated segmentation of structural MRI, transcranial magnetic stimulation, EEG and neurobehavioral assessment of implicit contextual memory-guided attention, the following new findings were abtained:

1. Hippocampal volume positively predicts implicit contextual memory-guided attention.
2. The hippocampus is involved in the unconscious forms of associative learning.
3. Disruption of DLPFC function improves implicit contextual memory-guided attention.

4. Reduction of beta-band oscillatory activity reflects reduced DLPFC mediated top-down modulation.

Taken together, these findings suggest a model in which the hippocampus interacts with the ventral frontoparietal attention network to translate implicit contextual memory into an attentional control signal. Importantly, during this process implicit contextual memory traces compete for attentional control with both top-down and bottom-up signals.

5.2 Integration into previous research

5.2.1 The hippocampus as a generator of modulatory inputs to attentional, perceptual and decision making systems

This thesis provides evidence that the hippocampus plays a central role in implicit contextual memory-guided attention. This finding contributes significantly to an emerging and unified explanatory framework for understanding hippocampal function. There are several reasons to believe that the hippocampus is not a locus for encoding conscious or declarative memories. Instead, this structure is specialized for the acquisition, and use of associative memory to bias attention, perception, and decision making.

First, our results add to the growing body of evidence indicating that certain forms of implicit memory are dependent on the hippocampus, including statistical learning, associative priming and implicit contextual learning (Chun & Phelps, 1999; Harrison, Duggins, & Friston, 2006; Turk-Browne et al., 2008; Hannula & Ranganath, 2009; Turk-Browne et al., 2010; Durrant, Cairney, & Lewis, 2012). These findings contradict the traditional view of hippocampal function which states that the formation of conscious or declarative memories critically depends on the hippocampus, while other forms of learning, that do not require conscious or deliberative access, depend on different brain systems, such as the striatum and cerebellum (Tulving & Schacter, 1990; Moscovitch.

1992). Notably, implicit contextual memory has perhaps provided the clearest example of how the hippocampus supports representations that are encoded and expressed in a totally implicit and automatic manner. Consequently, hippocampal involvement in implicit contextual memory strongly invalidates one of the most central aspects of the "multiple memory systems theory": the specialized role of the hippocampus in conscious memory.

Second, our result consistently support the "relational memory theory", and related models, which states that the encoding and binding of inter-item or item-context relationships is one of the most important functions of the hippocampus (Cohen & Eichenbaum, 1993; Eichenbaum et al., 1994; Henke, 2010). In this view, the evidence that implicates the hippocampus in declarative memory and the evidence that implicates the hippocampus in implicit forms of memory, are not essentially contradictory. The hippocampus appears to be necessary for all memory systems that require relational memory binding. Indeed, semantic, episodic, statistical, associative priming and contextual memory might be considered as subsets of relational memory. According to this view, hippocampal participation in implicit contextual memory suggest that the hippocampus provides a robust mechanism by which spatio-temporal regularities in our environment are intrinsically detected and encoded without consciousness. The rapid formation of efficient and flexible element-context relationships might be the basis of a self-organized process that allows the brain to interpret information about the environment.

Third, in recent years, cumulative evidence indicates that the hippocampus is involved in decision making (Johnson & Redish, 2007; Wimmer & Shohamy, 2012; Pfeiffer & Foster, 2013), reward, visual perception (Lee, Yeung, & Barense, 2012; Maguire & Mullally, 2013) and attention (Muzzio et al, 2009; Reas & Brewer, 2013). This contradicts the traditional view of this region as a module exclusively dedicated to mnemonic processes, instead of suggesting that the hippocampus plays a broader role in cognition. The link between the hippocampus and implicit contextual memory-guided attention is largely consistent with the notion that hippocampal-dependent mnemotechnic

representations can be used to directly modulate the processing of other systems (Shohamy & Turk-Browne, 2013). This emerging approach, known as “the memory modulation hypothesis”, argues that given the prominent and reciprocal anatomical connections between the hippocampus and several regions of the brain including dorsal and ventral PFC, striatum, thalamus, lateral parietal cortex, and visual cortex, the hippocampus is well situated to act as a locus for generating short- and long-term modulatory inputs to brains systems related with central aspects of cognition. According to this model, it has been suggested that the specific mechanism by which the hippocampus might modulate attentional, perceptual, or decision making systems relies on two important properties of the hippocampus. First, the hippocampus has an intrinsic tendency towards forming associative memory traces by encoding temporal and spatial relations between elements (Cohen & Eichenbaum, 1993; Eichenbaum et al., 1994; Henke, 2010). Second, subsequent interaction with one of those elements, automatically reactivate the whole network of elements that define the memory trace, process termed “pattern completion” (Norman & O’Reilly, 2003; Aminoff et al., 2013; Shohamy & Turk-Browne, 2013). This feature allows that the hippocampus evoking old memory traces during predictive behavior, integrating old memory traces with new ones to spread the positive value of reward across memories (Wimmer & Shohamy, 2012) (Chun & Phelps, 1999; Turk-Browne et al., 2010; Shohamy & Turk-Browne, 2013), influencing the probability of new learning (Shohamy & Wagner, 2008), and comparing expectations to outcomes during novelty detection (Kumaran & Maguire, 2007).

Taken together, the finding that the hippocampus supports implicit contextual memory-guided attention reported here provides news insights into the neurocognitive mechanisms of implicit memory-guided attention. First, the hippocampus continuously tracks the spatio-temporal co-occurrence of elements during visual search, and spontaneously and quickly encodes flexible element-context relationships. Second, over time, through pattern completion, the hippocampus reinstates those memory traces and sends modulatory inputs probably to the parietal areas of the fronto-parietal ventral attention network, biasing visual attention. Third, both the initial encoding and the expression of

those memory traces are totally automatic and unconscious. This is likely due to the fact that implicit contextual learning is characterized by short visual stimulus exposure, is not mediated by linguistic strategies, and memory traces are reinstated quickly. Consequently, during implicit contextual memory-guided attention, there is not enough time for visual cortex to become engaged in widespread recurrent interactions with frontal, prefrontal or temporal structures (Lamme, 2003). Therefore, no conscious visual experience is generated. Importantly, from this point of view, conscious experience is partially independent of either memory or attention.

5.2.2 The DLPFC and implicit contextual memory-guided attention: evidence of competitive interaction between neural systems subserving attentional control.

Multiple studies have demonstrated that the DLPFC is involved in voluntary top-down cognitive control. Particularly, it has been argued that it plays an specific role in the implementation of top-down control by actively maintaining task representations and demands (MacDonald, Cohen, Stenger, & Carter, 2000; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008) and suppressing automatic behaviors (Kübler et al., 2006; de Manzano & Ullén, 2012). Importantly, there is evidence that the reduction of top-down cognitive control through DLPFC deactivation facilitates implicit processing (Limb & Braun, 2008; Liu et al., 2012; Lee et al., 2013; Amer et al., 2016), suggesting that DLPFC can interfere with implicit learning. According to this evidence it seems logical to expect that DLPFC disruption improves implicit contextual memory-guided attention. However, this raises the question how does DLPFC-mediated top-down control specifically interferes with implicit contextual memory-guided attention. Here it is suggested that our result provides important evidence in favor of two complementary research streams that together give us novel insights into the implementation of contextual memory-guided attention in the brain.

First, based on the "dual-network architecture of top-down control" model (Dosenbach et al., 2008), the DLPFC is part of the fronto-parietal control network, a set of frontal and parietal regions associated with the rapid and flexible adjustment of top-down cognitive control. According to this model, the fronto-parietal control network include parts of the fronto-parietal dorsal attention network (the intraparietal sulcus and dorsal frontal cortex), suggesting that the fronto-parietal control network and the fronto-parietal dorsal attention network are closely interconnected in order to implement top-down cognitive control over visual attentional processes. Importantly, various studies have confirmed the competitive nature of the interactions between the fronto-parietal dorsal attention network and the fronto-parietal ventral attention network (Corbetta et al., 2000; Corbetta & Shulman, 2002; Yantis et al., 2002; Corbetta et al., 2008). Particularly, there is evidence that in in stimulus-driven attentional control the right ventral frontoparietal network (TPJ and VFC) redirects attention via connections with the FEFs. In endogenous control of attention, the fronto-parietal ventral attention network is suppressed by the fronto-parietal dorsal attention network (FEFs and IPs) to prevent stimulus-driven reorienting (Corbetta et al., 2000; Shulman et al., 2003; Corbetta et al., 2008). Taken together, these findings could be interpreted as evidence that the DLPFC both directly contributes to the initiation and adjustment of top-down attentional control, and is part of a brain network that potentially might interfere with bottom-up processing or any other process that involves the fronto-parietal ventral attention network.

Second, according to the "attention to memory model" (Cabeza et al., 2008; Ciaramelli, Grady, Moscovitch, 2008; Ciaramelli et al., 2010), the dorsal and ventral parietal parts of the fronto-parietal dorsal attention network and the fronto-parietal ventral attention network, respectively, play an analogous role in memory retrieval to those they play in attentional control. While (dorsolateral) PFC-dorsal parietal cortex interactions enable top-down capture of attention by voluntary retrieved contents, the interactions between MTL, including the hippocampus, and the ventral posterior parietal cortex might support bottom-up capture of attention by spontaneous and involuntarily retrieved contents. In this context, recent evidence indicates that the vPPC (including the TPJ) plays an

important role in implicit retrieval (Elman & Shimamura, 2011). From this view, vPPC signaling is needed to redirect attention towards either sensory-driven or hippocampally-driven signals. Thus, extending the distinction between ventral and dorsal memory retrieval mechanisms to the implicit contextual memory domain, here, we hypothesize that the hippocampus-TPJ interaction (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Poppenk & Moscovitch, 2011; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013) might be used to indicate the need to translate implicit contextual representations into attentional control signals. The right TPJ and VFC interactions integrate implicit contextual memory traces with incoming sensory information to supply attentional control signals to the fronto-parietal dorsal attention network.

Taken together, the interfering effect of DLPFC-mediated top-down cognitive control on implicit learning could be interpreted as evidence that DLPFC is part of an interactive top-down attentional control system that competes for limited neural resources with the fronto-parietal ventral attention network diminishing implicit processing capabilities. In particular, we propose that the “DLPFC TMS-induced facilitatory effect” on implicit contextual memory-guided attention observed here, might be caused by reduction of competition for neural resources between the top-down attentional control network and the hippocampus-TPJ-VFC network. By minimizing one of the most important sources of top-down signaling, reduced endogenous attentional control facilitates hippocampus-TPJ-VFC communication, enhancing the probability that implicit contextual memories be translated into attentional control signals.

5.2.3 Beta-band oscillatory activity: an index of DLPFC-mediated top-down cognitive control

In the present study, we observed that transient disruption of the DLPFC function by TMS significantly decreased task-related beta-band oscillatory activity (13-19 Hz, 140-370 ms). This finding provides several insights into the role of beta oscillations in top-down modulation of neural processing and expands our understanding of the competitive interaction between implicit

memory-guided attentional brain mechanisms and the top-down attentional control system.

Our finding is in agreement with previous studies investigating the effects of cTBS on brain oscillatory activity. Particularly, it has been observed that low beta-band oscillatory activity decreased bilaterally at frontal electrodes after cTBS over the left DLPFC (Woźniak-Kwaśniewska et al., 2014). Due to beta band oscillations depending mainly on the activity of pyramidal and fast-spiking inhibitory interneurons (Cardin et al. 2009; Kopell et al. 2011), this finding has been interpreted as evidence that the cTBS over left DLPFC reduces cortical inhibition (Woźniak-Kwaśniewska et al. 2014). Interestingly, it has been argued that because the rebound from inhibition plays a fundamental role in the genesis of low beta rhythms, this oscillatory activity is ideally suited for supporting the formation of endogenous self-sustaining neuronal assemblies that persist over time in the absence of recurrent input (Roopun et al. 2008; Kopell, Whittington, & Kramer, 2011). This suggests that low beta oscillations provide an intrinsic mechanism for supporting top-down cognitive control. Consequently, TMS-induced beta-band activity suppression may reflect disruption of the mechanisms for the formation of neural assemblies that convey top-down signals. Further support for the notion that beta oscillations are an important mechanism for implementing voluntary top-down cognitive control, comes from the “status quo” model (Engel & Fries, 2010). According to this view, reduced beta-band oscillatory activity is mainly related to exogenous, bottom-up processing, while enhanced beta-band oscillatory activity is linked to endogenous, top-down-controlled processing (Buschman & Miller, 2007; Pesaran et al., 2008). Thus, in this view, beta oscillations provide a physiological mechanism for actively preserving an endogenous cognitive set, or status quo, in the service of task representations and demands. Consistent with this perspective, it has been suggested that beta oscillations play a key role in regulating large-scale communication between the frontal cortex and other brain areas, including parietal areas, in order to drive top-down cognitive control (Buschman & Miller, 2007; Pesaran et al.. 2008). Furthermore, the “communication through coherence” model proposed that beta oscillatory

synchronization plays a central role in top-down attentional control by regulating the gain of the transmission of incoming sensory information (Engel et al., 2001; Fries, 2005; Fries, 2015). Indeed, it has been observed that attentional top-down influences mediated by low beta-band oscillations modulate directly feedforward stimulus-driven gamma oscillations in early sensory processing (Richter, Thompson, Bosman, & Fries 2017). Thus, low beta-band oscillations can directly influence high-frequency oscillations typically related with bottom-up processing and likely interfere with other forms of attentional control.

In short, these studies together with the present findings suggest that TMS-induced beta-band activity suppression likely reflects disengagement of top-down cognitive control, through diminished oscillatory synchronization in the fronto-parietal network. Because beta-band oscillatory activity should be higher when subjects engage in top-down strategies for learning (e.g., active search strategy) or require stronger top-down control in implicit contextual memory-guided attention, TMS-induced suppression of beta-band activity may reduce the probability of the formation of neural assemblies that convey top-down signals, eliminating endogenous influences over memory-driven and stimulus-driven processing. Under these circumstances, implicit contextual representations have a higher chance of biasing the processing of incoming sensory information.

5.2.4 A neurocognitive model for implicit memory-guided attention

Based on the current results and previous studies a neurocognitive model for implicit contextual memory-guided attention is proposed (see Fig. 7).

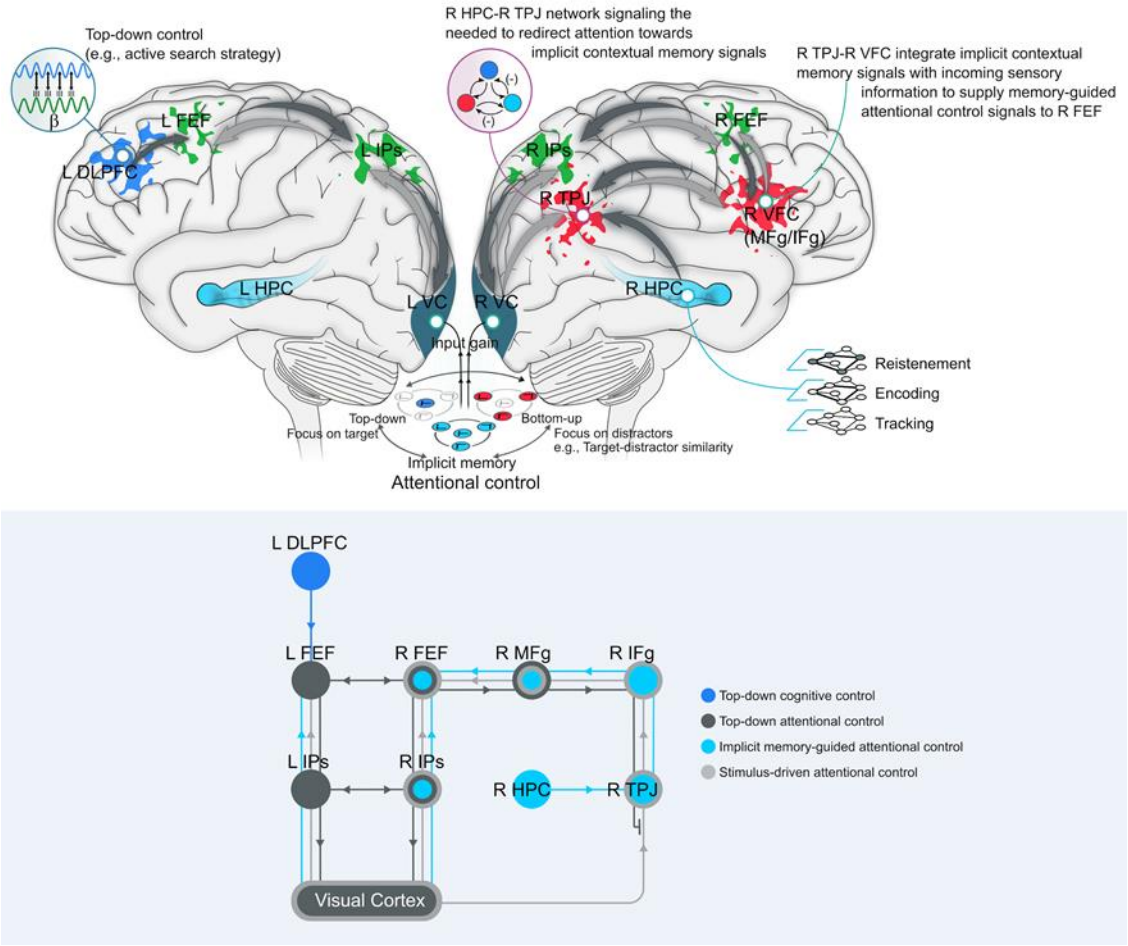

Figure 7. Model for the implicit memory-guided attentional control network, and its interaction with stimulus-driven and top-down attentional control networks. During implicit contextual memory-guided attention, the hippocampus reactivates implicit contextual memory traces and the R TPJ - R VFC network translates that into an attentional control signal and redirects attention via FEFs. At this point, top-down (e.g., active search strategy) and bottom-up (e.g., target-distractor similarity) influences compete with implicit contextual memory-guided signals for attentional control.

First, spatio-temporal co-occurrence of elements present in the environment tends to be continuously, spontaneously and unconsciously tracked and is encoded by the hippocampus. Second, over time, a new interaction with one of those elements, automatically reactivates the whole network of elements that

define the memory trace. Thus, the hippocampus reinstates implicit contextual memory traces in order to guide attention. Third, the hippocampus-TPJ interaction signals the need to redirect attention towards implicit contextual memory signals. Four, right TPJ and VFC interactions integrate implicit contextual memory signals with incoming sensory information to provide attentional control signals to the fronto-parietal dorsal attention network. Five, at this point, the implicit contextual memory-guided attentional system has to compete for limited neural resources with both the top-down and bottom up attentional control systems. Factors such as voluntary cognitive control (e. g., active search strategy), entails the generation of endogenous top-down attentional control signals mediated by low beta-band oscillations in the dorsal frontoparietal network. Similarly, factors such as distractibility (e. g., stimulus salience) are supported by bottom-up attentional control signals in the ventral frontoparietal network. Importantly, those top-down and bottom-up influences compete with implicit contextual memory-guided signals coming from the hippocampus-TPJ network for attention control. Five, if the competition is biased in favor of memory-guided control signals, then the gain of incoming sensory information in visual cortex is regulated via FEFs in support of implicit contextual representations, otherwise, top-down or exogenous attentional control signals may interfere with the expression of the implicit contextual memories.

From this view:

1. Hippocampal function goes beyond the participation in mnemonic processes such as encoding and reinstatement of implicit contextual memory traces. It acts as an important source of neuromodulatory inputs to parietal cortex in order to guide visuo-spatial attention.
2. Right hippocampus, right TPJ and right VFC act as a memory-driven network that translate implicit contextual memory into an attention control signal.
3. Implicit contextual memory-guided attention depends on competitive interactions with both top-down and bottom up influences.

5.3 Limitations

Although the aim of the study 1 was to specifically examine if hippocampal volume would positively predict contextual cueing performance, there are some limitations of the current design. The hippocampal system does not tend to work in isolation, additional factors may affect the encoding and expression of implicit contextual memory. Visual search facilitation in repeated contexts may involve reciprocal interactions between medial temporal lobe structures and both dorsal and ventral attentional networks (Hutchinson & Turk-Browne, 2012) and the striatum (Goldfarb et al., 2016). Consequently, voluntary control of attention, stimulus-response associations, and exogenous attention load may interfere with the encoding and expression of implicit memories (Manginelli et al., 2012; Schlagbauer et al., 2012; Annac et al., 2013; Lee et al., 2013; Goldfarb et al., 2016).

On the other hand, the study 2 has some limitations which have to be pointed out there. First, the study 2 does not allow for the source reconstruction of beta-band activity due to the EEG was recorded from 30 scalp electrodes, an insufficient number of electrodes to provide adequate accuracy in source estimation (Sohrabpour et al., 2015; Song et al., 2015). Another potential limitation of this study is that we did not have an enough controlled experimental design to examine if the facilitatory effect of TMS DLPFC on implicit contextual learning occur in the encoding, retrieval or both processes. Future research would benefit from incorporating this issue into the study design.

5.4 Future directions

The present doctoral thesis stress the importance of the morphology of hippocampus in implicit contextual memory-guided attention. Importantly, recent findings suggest that hippocampal volume reductions is one of the hallmark features of PTSD (Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Smith, 2005; Karl et al., 2006). Moreover, deficits in the processing of contextual information during fear learning have been hypothesized to contribute to post-traumatic stress disorder (Rudy et al; 2004; Brewin et al; 2007; Lang et al; 2009; Acheson et al; 2012). On a more fundamental level, I should expect that the impairment in hippocampal-dependent context fear learning observed in PTSD emerges from a general deficit in contextual processing. Therefore, future research should examine whether implicit contextual memory is

impaired in PTSD patients, and if there is a correlation between hippocampal volume and implicit learning of contextual information. In this dissertation, I show that disruption of DLPFC significantly improves implicit contextual learning. These results provide first causal evidence that the DLPFC plays an interfering role in implicit contextual memory-guided attention in the human brain. Future research is needed to determine the specific mechanisms by which DLPFC interacts with the brain systems that support implicit contextual memory-guided attention, including the hippocampus and the dorsal and ventral attentional networks. Furthermore, our study 2 is the first to shed light onto the relationship between brain oscillations and implicit memory guided attention and support the notion that beta-band oscillatory activity promotes DLPFC-mediated top-down control. This results can serve as a basis for future research to determinate how beta-band oscillations interact with sensory oscillations during implicit memory-driven processing.

6 SUMMARY

The intrinsic brain property to automatically detect and encode repeated regularities or contexts present in the environment is essential for organizing information about the environment and guides many aspects of our behavior, including attention. Decades of research into the neurocognitive mechanisms of attention have revealed that visual attention can be controlled by perceptually salient information (bottom-up) or by internal goals and expectations (top-down). However, recent findings have shown that implicit contextual memory (ICM) also plays an important role in guiding attention. Despite the importance of implicit contextual memory in cognition, it is unclear how the brain encodes and retrieves implicit contextual memories, translates them into an attentional control signal, and interacts with the ventral and dorsal frontoparietal attention networks to control deployment of visual attention. In this thesis, I answer a number of questions about the role of the hippocampus and the DLPFC in implicit contextual memory-guided attention. First, I combine automated segmentation of structural MRI with neurobehavioral assessment of implicit contextual memory-guided attention to test the hypothesis that hippocampal volume would predict the magnitude of implicit contextual learning. Forty healthy subjects underwent 3T magnetic

resonance imaging brain scanning with subsequent automatic measurement of the total brain and hippocampal (right and left) volumes. Implicit learning of contextual information was measured using the contextual cueing task. It was shown that both, left and right hippocampal volumes positively predict implicit contextual memory performance. This result provides new evidence for hippocampal involvement in implicit contextual memory-guided attention. Next, I used continuous theta burst stimulation (cTBS) combined with electroencephalography (EEG) to test whether transient disruption of the DLPFC would interfere with implicit learning performance and related electrical brain activity. I applied neuronavigation-guided cTBS to the DLPFC or to the vertex as a control region, prior to the performance of an implicit contextual learning task. It was shown that a transient disruption of the function of the left DLPFC leads to significant enhancement of implicit contextual memory performance. This finding provides novel causal evidence for the interfering role of DLPFC-mediated top-down control on implicit memory-guided attention. Additionally, it was shown that cTBS applied over the left DLPFC significantly decreased task-related beta-band oscillatory activity, suggesting that beta-band oscillatory activity is an index of DLPFC-mediated top-down cognitive control.

Together, these results shed light on how implicit memory-guided attention is implemented in the brain.

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8 CURRICULUM VITAE

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